Magellan Rx MANAGEMENT

Clinical Alert

OCTOBER 2015

Daraprim® for Toxoplasmosis

Pyrimethamine (Daraprim; Turing Pharmaceuticals) is an oral antiparasitic agent indicated to treat *Toxoplasmosis gondii* and prevent and treat acute malaria. Toxoplasmosis is a serious parasitic infection that can lead to life-threatening illness, such as encephalitis. It generally occurs in patients who are immunocompromised due to HIV/AIDS or cancer, and in infants born to women who have become infected during pregnancy. Transmission of the parasite is typically foodborne (uncooked contaminated meat), animal-to-human, and mother-to-child. According to the Centers for Disease Control and Prevention (CDC), over 60 million people in the United States are infected with the *Toxoplasma* parasite; the prevalence is much higher in other parts of the world.

Pyrimethamine, in combination with a sulfadiazine antibiotic, is the standard first-line treatment for toxoplasmosis. The manufacturer states that the majority of cases require 6 to 12 weeks of therapy; however patients diagnosed with encephalitis may need several months of therapy for secondary prophylaxis. Data supporting alternative regimens to treat toxoplasmosis are limited. Pyrimethamine, given with a sulfonamide, is not the therapy of choice to treat/prevent malaria.

Daraprim has been on the market since 1953. Although no patent limitations exist, there is no generic equivalent. Daraprim has changed manufacturer hands multiple times since 2010, each time incurring a price increase. In June 2015, Daraprim became available only through a special pharmacy program. In August 2015, Turing Pharmaceuticals acquired marketing rights to Daraprim and subsequently increased the price from $13.55 to $750 per oral tablet (based on Wholesale Acquisition Cost). At this price, the annual cost of treatment could be hundreds of thousand of dollars for some patients. Concerns of treatment delays exist due to the high price and method of distribution. If a delay in obtaining the drug is experienced, trimethoprim-sulfamethoxazole is recommended as an alternative to the standard therapy, for patients with no sulfa allergy. In response to public outcry, Turing has decided to lower the price of Daraprim in the coming weeks and modify the distribution channel; final price and distribution strategies have not been announced.

Large pricing increases after a change in marketing rights have also been displayed for other drugs that have been on the market for many years; some examples include cycloserine, used to treat tuberculosis (Rodelis Therapeutics), the antibiotic doxycycline, and the cardiovascular agents Isuprel® (isoproterenol; Valeant) and Nitropress® (nitroprusside; Valeant).

AASLD Overview of Cost Considerations for HCV

In the quickly changing field of antiviral therapy for hepatitis C virus (HCV), one of the most common challenges is access to care due to high drug cost. The American Association for the Study of Liver Diseases (AASLD) recently added a new section to their HCV guidance to review cost considerations related to HCV treatment. In this section, the concepts of drug cost, reimbursement, cost-effectiveness, and affordability are defined and discussed. Also included in this section is a review of the available cost-effective studies for treatment regimens for each HCV genotype. The HCV recommendations for treatment do not currently utilize cost-effectiveness analyses.

Drug Information Highlights

- The Food and Drug Administration (FDA) is warning that dipeptidyl peptidase-4 (DPP-4) inhibitors, alogliptin, linagliptin, saxagliptin, and sitagliptin, may cause severe, disabling joint pain. Symptoms of joint pain have been reported from 1 day to several years after starting a DPP-4 inhibitor; however, symptoms appear to subside after discontinuation of the medication. Health care professionals (HCPs) are urged to consider DPP-4 inhibitors as a source of joint pain and to stop the agent if needed. Patients taking a DPP-4 inhibitor who experience joint pain should not stop their medication, but should contact their HCP immediately. DPP-4 inhibitors are indicated for the management of type 2 diabetes mellitus.
- Egalet has announced the launch of Oxaydo™, an immediate-release (IR) oral formulation of oxycodone. Oxaydo (formerly known as Oxecta™) is the first and only IR oxycodone available designed to deter abuse via snorting.
- Ticagrelor (Brilinta®; AstraZeneca) has been approved for patients with a history of MI beyond the first year. With this expanded indication, ticagrelor is approved to reduce the rate of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or history of MI. The label indicates that ticagrelor is superior to clopidogrel for at least the first 12 months following ACS. The FDA also approved a new Brilinta 60 mg tablet strength. Therapy should begin with a 180 mg loading dose, followed by 90 mg twice daily for the first year after ACS event. After 1 year, the dose should be reduced to 60 mg twice daily.
- The FDA is investigating the use of tramadol in patients 17 years of age and younger due to the rare but serious risk of slowed or difficult breathing. This risk may be increased in pediatric patients receiving doses for post-operative pain control following tonsillectomy or adenoid surgery and has been reported following just one dose. While tramadol is not FDA-approved for use in pediatric patients, there are data supporting its use in this population. The FDA urges HCPs to use alternative medications for pain control in pediatric patients.
- The carbamazepine derivative anticonvulsant, eslicarbazepine (Aptiom®), received an expanded indication as monotherapy for partial-onset seizures. Eslicarbazepine was previously indicated only as adjunctive therapy.

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FDA Safety Communication for Clozapine Related Neutropenia

The Food and Drug Administration (FDA) has changed the requirements for monitoring, prescribing, and dispensing of the atypical antipsychotic agent, clozapine, in order to reflect current knowledge of safety concerns regarding neutropenia. In their recent safety communication, the agency outlined the new monitoring recommendations for neutropenia associated with clozapine use. Neutropenia should now be monitored by the absolute neutrophil count (ANC) only, rather than in conjunction with the white blood cell count. The new requirements allow for a lower ANC, which will permit treatment to continue for more patients. Additionally, an algorithm for monitoring ANC for patients with benign ethnic neutropenia (BEN) has been added, where previously patients with BEN were not eligible for clozapine treatment. The FDA also approved a new shared risk evaluation and mitigation strategy (REMS) program, Clozapine REMS Program, which will replace the six existing registries maintained by individual clozapine manufacturers. Patients currently taking clozapine will be automatically transferred to the new program. In order to prescribe and dispense clozapine, prescribers and pharmacies will be required to be certified in the Clozapine REMS Program starting October 12, 2015. More information about the Clozapine REMS Program is available at: www.clozapinerems.com. Clozapine brand products include Clozaril® (Novartis), Fazaclo®, and Versacloz® (both Jazz).

Cardiovascular Outcomes for Empagliflozin

The EMPA-REG OUTCOME trial was a placebo-controlled, double-blind trial designed to determine non-inferiority of empagliflozin (Jardiance®; Boehringer Ingelheim) compared to placebo on CV morbidity and mortality in patients with type 2 diabetes (T2DM) who were at high risk for CV events. Empagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor which has been shown to reduce rates of hyperglycemia in patients with T2DM by decreasing renal glucose reabsorption. The primary endpoint of the study was a composite of death from CV causes, nonfatal MI, or nonfatal stroke. The secondary endpoint was a composite of the primary endpoint plus hospitalization for unstable angina. A total of 7,020 adult patients were randomized to receive 10 mg or 25 mg empagliflozin, or placebo once daily in addition to standard care. Average length of therapy was 3.1 years. The primary endpoint occurred in a significantly lower percentage of patients in the combined empagliflozin group than in the placebo group (10.5% versus 12.1%; $p<0.001$ for non-inferiority). The key secondary outcome also occurred in proportionately less patients who received empagliflozin than those who received placebo (12.8% versus 14.3%; $p<0.001$ for non-inferiority). Patients in the empagliflozin group had an increased rate of genital infections; no other differences in adverse events were observed. The authors concluded that patients with T2DM who are at high risk for CV events had a lower rate of composite CV outcome and death from any cause, when treated with empagliflozin as compared to placebo, in addition to standard care. It is unclear at this time whether the positive CV outcomes data reported with empagliflozin is a SGLT2 class effect.

FDA Safety Warning: Bone Fracture linked to Canagliflozin Use

The FDA strengthened the warning for the SGLT2 inhibitor canagliflozin (Invokana®, Invokamet®; Janssen) related to the increased risk of bone fractures and added new information to the drug label about decreased bone mineral density (BMD). The risk of bone fractures was previously listed in the adverse reactions section of the label. However, data from several clinical trials indicate an increased risk of bone fracture with fractures occurring as early as 12 weeks after starting canagliflozin therapy. This information is now reflected in the warnings section of the label. Additionally, the results of a 2-year placebo-controlled, FDA-mandated, post-marketing trial that evaluated changes in BMD in older patients, showed that canagliflozin caused greater loss of BMD at the hip and lower spine than placebo. The FDA is continuing to evaluate the risks of bone fractures for other agents in the SGLT2 inhibitor class and HCPs are encouraged to report side effects via FDA's MedWatch.

- The FDA has expanded the indication for eltrombopag (Promacta®; Novartis) to include the treatment of thrombocytopenia in pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia who have had insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag was previously approved for this indication only for those aged 6 years and older. Prior approved indications include thrombocytopenia in patients with chronic hepatitis C. A new 25 mg oral suspension has also been approved for pediatric use.
- Adalimumab (Humira®; Abbvie) was granted orphan drug designation for the treatment of moderate-to-severe hidradenitis suppurativa (HS), a chronic inflammatory skin disease characterized by painful lesions around the armpits, groin, buttocks, and under the breasts. Humira is also indicated to treat rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, and ulcerative colitis.
- The FDA approved Synjardy®, a combination of empagliflozin and metformin to improve glycemic control in adults with T2DM that is not controlled with a regimen containing at least one of the drugs. This Boehringer Ingelheim fixed-dose combination is dosed twice daily.

Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **October 2015:** Xeljanz®; tofacitinib; oral Janus Kinase inhibitor; moderate to severe plaque psoriasis; Pfizer/Takeda.
- **October 2, 2015:** Keytruda®; pembrolizumab; intravenous (IV) anti-PD1 antibody; non-small cell lung cancer; Merck.
- **October 21, 2015:** patiromer; oral potassium binder; hyperkalemia; Relypsa.
- **October 23, 2015:** Belbuca; buprenorphine; oral opioid partial agonist; moderate to severe chronic pain; Endo/BioDelivery Sciences.
- **October 23, 2015:** Evomela; melphalan HCl; IV alkylating agent; multiple myeloma; Spectrum.
- **October 24, 2015:** MM-398; irinotecan; IV topoisomerase I inhibitor; metastatic pancreatic cancer; Merrimack/Baxter.
- **October 25, 2015:** lifitegrast; ophthalmic CD11a/CD18 antagonist; dry eye; Shire.
- **October 27, 2015:** T-VEC; talimogene laherparepvec; intralesion injectable oncolytic virus; non-resectable melanoma; Amgen.
- **October 28, 2015:** Yervoy®; ipilimumab; IV anti-CTLA-4 antibody; melanoma; Bristol-Myers Squibb.
- **Quarter 4, 2015:** brivaracetam; oral/IV anticonvulsant; partial onset seizures; UCB.
- **Quarter 4, 2015:** Ultibro Breezhaler; indacaterol/glycopyrronium; inhaled long-acting beta-2 agonist/long-acting muscarinic antagonist; Novartis.
- **Second Half 2015:** necitumumab; anti-EGFR antibody; non-small cell lung cancer; Eli Lilly.
- **Second Half 2015:** Strensiq®; asfotase alfa; SC alkaline phosphate enzyme; hypophosphatasia; Alexion.

AHA Discusses MDD/Bipolar Disorder CVD Risk in Adolescents

Major depressive disorder (MDD) and bipolar disorder (BD) together affect about 10% of adolescents in the U.S. In 2011, the American Heart Association (AHA) identified several medical conditions that put this population at moderate to high risk for early cardiovascular disease (CVD). Conditions were identified based on pathophysiological evidence for arterial dysfunction that indicated accelerated atherosclerosis before age 30 years and included cancer survival, chronic kidney disease, chronic inflammatory disease, congenital heart disease, diabetes mellitus, familial hypercholesterolemia, heart transplant, and Kawasaki disease. Recently, AHA determined that MDD and BD also fit the criteria for moderate risk and advise that they be similarly managed.

The AHA released a statement that discusses the link between pediatric MDD and/or BD and premature CVD, including behavioral and pathophysiological mechanisms and the roles of mood-stabilizing drugs. It provides an algorithm for managing patients with increased CVD risk and advises that all adolescents diagnosis with MDD or BD should be accessed for other CV risk factors, such as elevated blood pressure, smoking history, and family history of early CVD. Patients are considered to be at moderate risk if zero or 1 risk factor is identified, whereby CV management targets such as body mass index (BMI) ≤ 90th percentile, blood pressure (BP) ≤ 95th percentile, and LDL-C ≤ 130 mg/dL are appropriate. Patients with 2 or more risk factors are regarded as high risk for developing CVD and should be managed with stricter goals, including BMI ≤ 85th percentile, BP ≤ 90th percentile, and LDL-C ≤ 100 mg/dL.

Future studies are needed in both adults and pediatrics to determine whether other psychiatric conditions, such as anxiety disorders, have an impact on CVD risk.

Injectable Risperidone for Recent Onset Schizophrenia

Schizophrenia has been historically difficult to treat; with several studies demonstrating that nonadherence to medications contributes to the return of psychotic symptoms and relapse. Patients with schizophrenia often have poor insight to the importance of antipsychotic medication adherence, which makes taking oral medications on a daily basis unpredictable. Long-acting injectable (LAI) second-generation antipsychotics have the potential to increase compliance and reduce the rate of relapse.

A recent 12-month clinical trial by Subotnick, et al, included 86 patients randomized to oral risperidone or to LAI risperidone. The study included patients who were diagnosed with schizophrenia, schizoaffective disorder, depressed type, or schizophreniform disorder, and had a recent onset of psychotic illness within the past 2 years. In addition to risperidone therapy, patients in each group were also randomized to receive cognitive remediation to improve cognitive functioning or healthy-behaviors training to improve lifestyle habits. The primary outcome was psychotic exacerbation and/or relapse with the expanded 24-item version of the Brief Psychiatric Rating Scale (BPRS) used to rate patients every 2 weeks. The psychotic exacerbation and/or relapse rate was significantly lower for the LAI risperidone group compared with the oral group (5% versus 33%). Also, LAI risperidone was found to better control levels of delusions and hallucinations. The cognitive remediation and healthy-behaviors training had no impact on psychotic relapse or symptom control, or hospitalization rates.

Based on the results of this trial, starting a long-acting injectable antipsychotic after a recent onset of schizophrenia is more effective than starting an oral antipsychotic. Apparent benefits include ease of medication adherence, which is vital during the early stages of schizophrenia when insight of therapy compliance is notably low. Using long-acting injectables earlier in the course of the disease may very well improve patient outcomes and reduce relapse rates in this extremely fragile population.

Clonidine Use in Addiction Management

Many of those afflicted with an addiction can abstain from their drug of choice through a variety of methods; voluntary or involuntary (via rehabilitation program, incarceration, etc.). However, once they return to an uncontrolled setting the likelihood of a relapse is very high. Most often relapses occur long after the acute withdrawal effects have ceased. When and why relapse occurs is often unpredictable, making it very difficult to study.

In a recent double-blind, placebo-controlled study by Kowalczyk, et al., new data supports the hypothesis that stress influences relapse and that if stress is reduced so is the rate of relapse. The hypothesis of stress as a key component of relapse is supported by clinical reports and animal studies that have revealed that alpha-2 adrenergic receptor agonists lessen stress induced relapse.

Clonidine, an alpha noradrenergic agonist, is commonly used during the detoxification stage of addiction treatment; however, it is currently unknown how and why clonidine reduces drug seeking behavior.

In the Kowalczyk study, 118 patients that had achieved abstinence from opioids for 5 to 6 weeks with buprenorphine treatment were randomly assigned to continue buprenorphine for 14 weeks, with or without clonidine. Data was collected via handheld electronic devices 4 times daily and focused on the participant's mood and cravings. Lapse was defined as any opioid-positive or missed urine test, and relapse was defined as 2 or more consecutive lapses. The clonidine group had an extended duration of abstinence (34.8 versus 25.5 days), but both groups had similar relapse rates overall. However, through extensive symptom monitoring the investigators concluded that clonidine reduced the temporal association with stress and opioid cravings; which supports the hypothesis of clonidine decreasing stress.

Although there is a vast amount of information from controlled studies on drug abuse, there is very little from a non-controlled setting. The factors that lead to relapse could provide a wealth of knowledge for researchers. Future studies are needed that use rigorous data collection techniques, such as those employed in this study, to provide a better understanding of relapse in a natural environment. Study authors concluded that clonidine may be useful to reduce the symptoms of opioid withdrawal and also as an adjunctive maintenance treatment to increase the duration of abstinence.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
rolapitant	Varubi™	Rolapitant (Varubi), a substance P/neurokinin 1 (NK1) receptor antagonist, was FDA approved in combination with other antiemetic medications to prevent delayed phase chemotherapy-induced nausea and vomiting in adults. Concurrent use with thioridazine is contraindicated. Rolapitant is approved as a 90 mg oral tablet. The recommended dosage is 180 mg administered 1 to 2 hours prior to chemotherapy along with dexamethasone and a 5-HT3 receptor antagonist.	Tesaro	FDA NDA Approval 09/01/2015
aspirin extended- release	Durlaza™	Durlaza, a 24-hour extended-release formulation of aspirin, was approved for the secondary prevention of stroke and acute CV events in patients with a history of stroke or acute cardiac event. It is not indicated for the acute treatment of MI or before percutaneous coronary intervention; immediate-release aspirin should be used in these cases. Durlaza is approved as a 162.5 mg capsule with a recommended dose of one capsule once daily.	New Haven	FDA NDA Approval 09/04/2015
recombinant blood coagulation factor VIII	Nuwiq®	The FDA approved the antihemophilic factor Nuwiq, which is indicated in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management of bleeding and routine prophylaxis to reduce the frequency of bleeding episodes. Nuwiq is not indicated to treat von Willebrand disease. Safety and efficacy have not been established in children < 2 years of age. Nuwiq is approved as a lyophilized powder for reconstitution in single use vials containing 250 IU, 500 IU, 1,000 IU and 2,000 IU factor VIII potency. Prophylaxis dosing for patients 12 years of age and older is 30-40 IU/kg infused IV every other day; for those 2 to 11 years infuse 30-50 IU/kg every other day or 3 times per week. On-demand dosing depends upon the type of bleeding episode.	Octapharma	FDA BLA Approval 09/04/2015
uridine triacetate	Xuriden™	Uridine triacetate, a pyrimidine analog, is the first FDA approved treatment for hereditary orotic aciduria, a rare pediatric metabolic disorder with only 20 known cases worldwide. Xuriden was granted orphan drug designation. There are no contraindications, warnings or adverse events reported with uridine triacetate. The recommended initial dose is 60 mg/kg once daily; which can be increased to 120 mg/kg daily based on orotic acid levels, red or white blood cells indices, or other signs of disease progression. Xuriden is approved as a 2 g packet containing oral granule that is administered with food, milk, or infant formula.	Wellstat	FDA NDA Priority Approval 09/04/2015
cariprazine	Vraylar™	Cariprazine (Vraylar), an atypical antipsychotic, was approved for the treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder. Cariprazine carries the same boxed warning as other atypical antipsychotics for increased mortality in elderly patients with dementia-related psychosis. Common side effects include extrapyramidal side effects including akathisia, tremors, slurred speech, restlessness and involuntary muscle movement. The initial dose for both indications is 1.5 mg daily. The recommended daily maintenance doses for schizophrenia and bipolar mania are 1.5 mg to 6 mg and 2 mg to 6 mg, respectively. Cariprazine strengths include 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules.	Forest	FDA NDA Approval 09/17/2015
trifluridine/ tipiracil	Lonsurf®	FDA approved Lonsurf, a combination of trifluridine, a nucleoside metabolic inhibitor and, tipiracil, a thymidine phosphorylase inhibitor, for the treatment of metastatic colorectal cancer in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Complete blood count should be monitored at the start of and throughout the course of therapy. The recommended dose is 35 mg/m^2 twice a day on days 1 to 5 and days 8 to 12 of each 28-day cycle to be taken within 1 hour after morning and evening meals. It is approved in two oral tablet strengths of trifluridine/tipiracil: 15 mg/6.14 mg and 20 mg/8.19 mg.	Taiho Oncology	FDA NDA Approval 09/22/2015
insulin degludec and insulin degludec/ insulin aspart	Tresiba® and Ryzodeg® 70/30	The FDA approved 2 insulin agents, the long-acting insulin degludec (Tresiba) and its combination with a rapid-acting insulin, insulin degludec/insulin aspart (Ryzodeg 70/30). Both products are indicated for the treatment of adults with T1DM or T2DM. Tresiba is self-administered SC once daily at any time of day. Ryzodec 70/30 is self-administered SC once or twice daily with any main meal. The most common adverse effects include hypoglycemia, allergic reactions, injection site reactions, and weight gain. Both products are approved as 3 mL prefilled FlexTouch® pens; Tresiba as 100 and 200 unit/mL that allow maximum doses of 80 and 160 units per single injection and Ryzodeg as a 70:30 ratio of insulin degludec and insulin aspart. Availablility is expected in first quarter 2016.	Novo Nordisk	FDA NDA Approval 09/25/2015

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